REMARKS

Applicants have canceled claims 1-11, 13, 15, 18-24, 26-30, 35, 40-42, and 45-48. Claims 12, 14, 16, 17, 25, 31-34, 36-39, 43, 44, 49, and 50 are pending. The claims are amended to more specifically define the components in the combination, to supplement functional language with specific activity, and to delete terms objected to by the Examiner. Support for the definition of a first compound as one that "activates GP130" can be found throughout the specification and particularly at page 8, lines 8-10. The selection of LIF as the first compound is supported in the original claims and throughout the specification, particularly at page 8, lines 10-11. Support for the definition of a second compound as one that "is an inhibitor of MEK" or "inhibits MEK" and for the selection of PD098059 and U0126 as the second compound can be found in the original claims and throughout the specification and particularly at page 5, lines 27-31, page 6, lines 4-9 and page 8, lines 5-7. Accordingly, no new matter has been added and Applicants respectfully request entry of the amendments.

Priority

The Examiner notes that Applicants have not filed a certified copy of priority applications PCT/GB99/03031 and GB 9819912.8. Applicants respectfully point out that PCT/GB99/03031 is not a priority application but is, rather, the international stage of the present U.S. national stage application. Moreover, a certified copy of GB 9819912.8 was filed with the International Bureau in PCT/GB99/03031. This priority application should have been transmitted to the U.S. receiving office along with the application upon entry into national phase. Applicants have attached a copy of GB 9819912.8 as a courtesy to the Examiner.

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Drawings

The Examiner has noted that drawings have been specifically described but not included in the application. Applicants request permission to amend the application to include the referenced drawings. Because the drawings are described in the specification in great detail at page 13, line 24 to page 17, line 5, Applicants submit that an amendment to include the actual drawings themselves into the specification does not add new matter. Applicants submit a draft set of Figures 1-8 with this response. Upon favorable consideration by the Examiner, Applicants will amend the application to include Figures 1-8.

Rejection under 35 U.S.C. §112, first paragraph

The Examiner has rejected the pending claims as allegedly not enabled by the specification. Specifically, the Examiner contends that the structure or function of (1) the IRES-β-go reporter gene inserted within the oct-4 gene locus, (2) the ZIN40 cells, and (3) the IOUD2 ES cells are not described in the application. The Examiner further contends that there is no correlation between the genetically altered ES cells described in the examples and normal ES cells. The Examiner concludes that it would require undue experimentation to practice the claimed invention. Applicants traverse.

Applicants respectfully submit that one of skill in the art would understand the structure and function of the constructs and modified ES cells described in the specification to exemplify the methods of the invention. Applicants further submit that following the teaching of the specification in combination with what is known in the art, the person of ordinary skill would be able to practice the invention without undue experimentation.

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The constructs used to exemplify the methods of the of the invention are of a type known in the art. See, e.g., United States Patent 6,150,169. Using the constructs as described, the reporter gene is expressed, for example, under control of the Oct 4 promoter. Oct 4 expression is known to be limited to ES cells, and hence expression of the reporter indicates presence of ES cell phenotype. See, e.g., page 21, lines 30-32, where the specification explains that expression of the reporter is restricted to ES cells.

As a further example that one of skill in the art would understand the structure and function of the constructs and cells described in the application, Applicants direct the Examiner's attention to the attached article by Mountford and Smith which describes how to make the IRES-containing constructs used in the invention. This paper also confirms, at page 182, right column, that the cell line ZIN40 is an ES cell line.

The examples recited in the specification show that an inhibitor of MEK, on its own, or in combination with gp130 activation, enhances self renewal of ES cells. The results reported at page 23 show that the presence of a MEK inhibitor increases self renewal in response to gp130 activation - see lines 13-15, where a dose-dependent increase in self renewal is described. The results on page 26 (lines 24-26) show that the presence of a MEK inhibitor increased the number of undifferentiated cells, i.e. ES cells.

Applicants submit the attached article by Williams et al. to provide a further example of a MEK inhibitor which was available at the filing date of this application. WIlliams et al. describes Ro-2210 as a selective inhibitor of MEK1.

Contrary to the Examiner's assertion, the cells used in the examples are representative of normal ES cells. They have been shown in the examples of the

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application to contribute to chimaeras. Contribution of the ZIN40 ES cells to chimaeras is disclosed in example 1, page 19, at lines 26-28 and confirmed on page 24, lines 20-22. Consequently, the results described in the specification can indeed be extended generally to ES cells. The ES cell lines used are truly representative of "normal" ES cells, the MEK inhibitor used is representative of MEK inhibitors, and the gp130 activator used is representative of gp130 activators.

Accordingly, Applicants request the rejection under 35 U.S.C. §112, first paragraph be withdrawn.

Rejection under 35 U.S.C. §112, second paragraph

The pending claims stand rejected as allegedly indefinite. Specifically, the Examiner contends that it is unclear whether the first and second compound may be the same or if they must be different. Applicants disagree with the pending claims are indefinite for this reason, but have amended the claims to make it clear that the first and second compounds (as well as the third and forth compounds) are different.

The Examiner further contends that the metes and bounds of compounds that "promote propagation or survival of ES cells" cannot be determined because the distinction between propagation and survival is unclear. Applicants have amended the claims to delete reference to "survival."

The Examiner further contends that the metes and bounds of compounds that "inhibit propagation or survival of cells other than ES cells" cannot be determined because the specification and the art at the time of filing did not teach any such compounds. Applicants disagree.

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The specification clearly identifies MEK inhibitors as inhibitors of the invention (page 6, lines 5-7) and further states that these inhibitors selectively inhibit a signaling pathway essential to propagation of cells other than ES cells leading to selective death or growth inhibition of differentiated cells (page 8, lines 1-4). Many MEK inhibitors were known as of the filing date of the application.

The Examiner states that the metes and bounds of (1) compounds that "selectively inhibit" and (2) of signaling pathways that are "essential to propagation" cannot be determined. These terms have been eliminated from the claims.

The Examiner contends that "cytokines that activate gp130" cannot be determined and that it is unclear if LIF is encompassed by the phrase and if cytokines other than LIF are encompassed by the phrase. Applicants traverse.

LIF is known to act through a LIF receptor that activates GP130. Several other such activators of gp130 were known prior to the filing date of the application. The specification identifies LIF and the combination of IL-6 and sIL-6R. As a result, applicants do not believe that there is any ambiguity associated with the term "cytokines that activate gp130." LIF and other cytokines are known to those of skill in the art to be activators of gp130.

The objections to claims 18, 26, 28, and 35 are moot in view of Applicants' cancellation of these claims.

Claims 25, 38, and 43 have been amended to remove the language objected to by the Examiner. The Examiner contends that it is unclear whether claim 43 encompasses genetic alteration. Applicants direct the Examiner's attention to Example

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3 of the application which describes expression of a transgene encoding a MEK inhibitor in ES cells.

In view of the amendments, Applicants request that the rejection under 35 U.S.C. §112, second paragraph be withdrawn.

Rejection under 35 U.S.C. §102(a)

The pending claims stand rejected as allegedly anticipated by Niwa et al. *Genes and Development* 12:2048-2060 (1998) ("Niwa"). Applicants note that Niwa is not work of another, but rather is work performed at the direction of inventors Tom Burdon and Austin Smith. Accordingly, the rejection under 35 U.S.C. §102(a) is not proper.

Moreover, Niwa does not anticipate the claimed invention because it merely observes that a known MEK inhibitor does not inhibit stem cell colony formation in response to LIF. This teaching is merely the absence of a negative - namely that the MEK inhibitor does not inhibit ES colony formation.

Niwa does not teach or suggest a synergy between an activator of gp130 and a MEK inhibitor which promotes propagation of ES cells as required in claims 12, 14, 16, 17, and 50. The basis of this synergy is set forth, e.g., in the examples and particularly at page 24. The results described here show the presence of the MEK inhibitor enhances the response of ES cells to the gp130 activator LIF. Less activator of GP130 is needed due to the addition of the MEK inhibitor to promote propagation. This can be seen in the example reported at the top of page 24, wherein less LIF is required due to the presence of PD 098059. There is no teaching or suggestion of this in Niwa.

Similarly, Niwa does not describe a culture medium having the components required by claims 25, 31, 32, and 33. It is understood by those of skill in the art that a

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culture medium contains factors suitable for culture of cells, typically in aqueous solution, but that the culture medium itself does not contain cells. In other words, the culture medium is designed for culture of ES cells, in that it is suitable for culture of ES cells when these cells are added to the medium, but the medium itself does not include those cells. This is readily apparent from the specification. See, e.g., page 8, lines 17-20, which refers to medium that is for culture of ES cells. Similarly, the passage bridging pages 8 and 9 refers to culturing cells in the presence of the culture medium - thus, a clear distinction is made between the medium and the cells which are then cultured in the medium. Likewise, a distinction is made in the examples between the medium and the cells - see, e.g., page 17, lines 11-13.

Claims 34, 36, 39, and 49 recite a step of maintaining cells in the presence of first and second compounds, dissociating the cells and then maintaining the dissociated cells in the presence of third and fourth (which can be the same as first and second) compounds. Niwa does not teach or suggest these steps. Niwa merely states that stem cell colony formation is not inhibited in the presence of LIF. There is no dissociation step in Niwa. There is no subsequent culture in the presence of third and fourth compounds.

Similarly, claims 37 and 38 recite a first culture in the presence of a MEK inhibitor, then a dissociation step and then a second culture in the presence of a MEK inhibitor. Neither the dissociation nor the subsequent culture is seen in Niwa.

Finally, Niwa does not express any transgene in his ES cells as required by claims 43 and 44.

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In view of the many distinctions between Niwa and the claimed invention, Applicants respectfully submit that the claims are not anticipated by Niwa and request that the rejection under 35 U.S.C. §102 be withdrawn.

In view of the foregoing amendments and remarks, Applicants request reconsideration and reexamination of this application and the timely allowance of the pending claims.

Applicants believe that any extension of time required for entry of this response is accounted for by the accompanying Petition. However, in the event of an error, please grant any additional extensions of time required to enter this response and charge any additional fees due to deposit account 06-0916.

Respectfully submitted,

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